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Improving the bioavailability APIs for delivery in oral solid dosage forms

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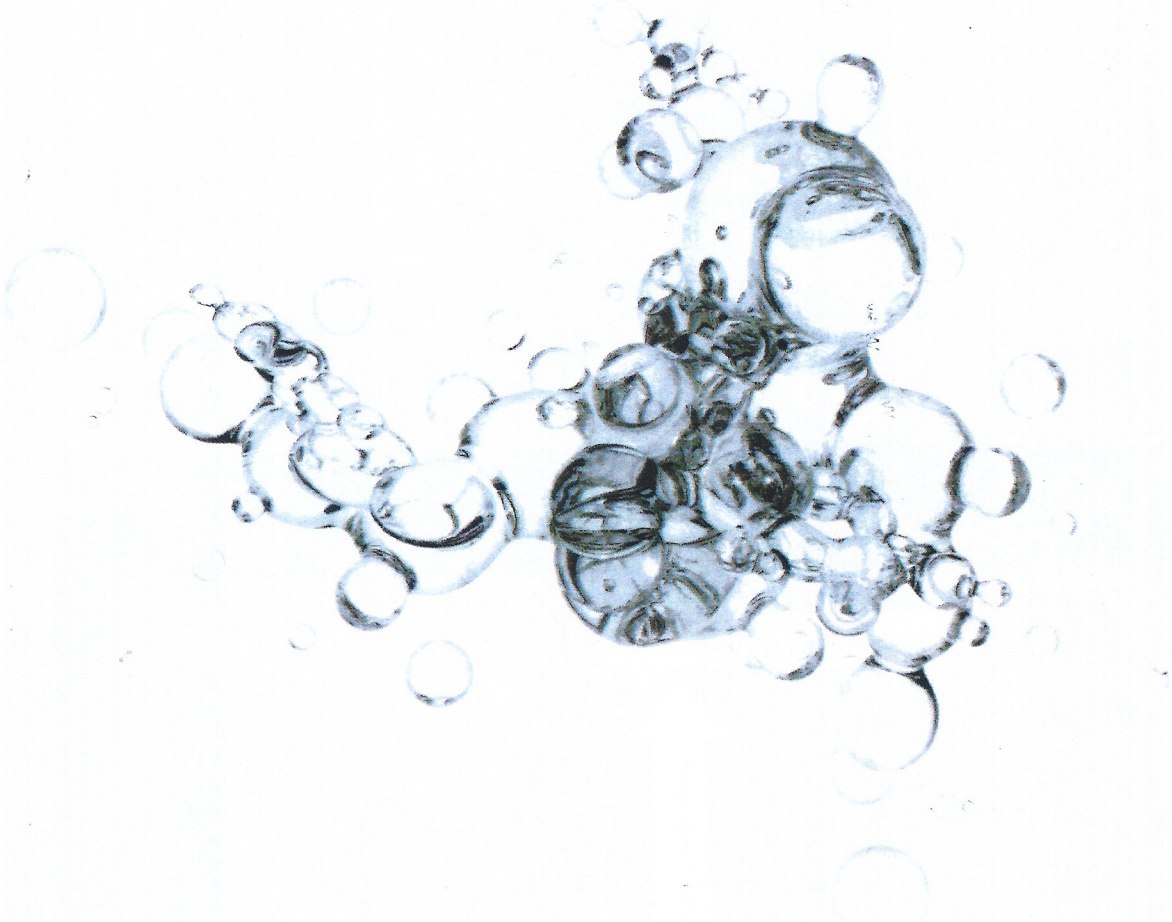


The bioavailability of an active pharmaceutical ingredient (API) depends on its chemical, biological, and physical properties. Good aqueous solubility is a key consideration to obtaining a bioavailable product. This article summarizes some of the techniques used to improve solubility and/or absorption. They include modifying the chemical structure, changing the physical form, reducing the particle size, and using fit-for-purpose excipients.

Delivering medicine orally via a tablet or capsule is a simple and easy way to administer APIs. Both solid dosage forms offer convenience, boost patient compliance, generally offer good stability profiles, provide accurate doses, and are easy to produce.

Historically, the speed of drug development was tied to the discovery of compounds with high biological activity and a strong affinity for receptor sites. More recently, pharmacokinetic factors such as absorption and permeability across the gastrointestinal (GI) epithelium have become key considerations.

An API's therapeutic effectiveness depends on its bioavailability and, ultimately, on its solubility. If an API is poorly water soluble, then it cannot get into solution. If it is not in solution, it cannot be absorbed by the body. In fact, poor aqueous solubility leads to inadequate and variable absorption via the GI tract and that diminishes efficacy.

Optimizing an API's solubility and bioavailability is one of the top challenges for formulators in the pharmaceutical and biotech industries. Furthermore, overcoming the challenge almost always increases development costs, lengthens development timelines, and raises the potential for delays in regulatory approval.

Poorly water-soluble or hydrophobic new chemical entities (NCEs) have dominated drug discovery programs for years. According to some estimates, nearly half of the drug products currently on the market have shown aqueous solubility issues. Additionally, a large number of the NCEs in early development show poor aqueous solubility.

Assessing bioavailablity

The Biopharmaceutics Classification System (BCS) was developed to help characterize solubility and permeability issues. It divides APIs into four categories, or classes. Class 1 APIs demonstrate high solubility and high permeability. Class 2 APIs have low solubility and high permeability. Class 3 APIs have high solubility and low permeability. Class 4 APIs exhibit both low solubility and low permeability (Figure 1). In general, API absorption, bioavailability, and the pharmacokinetic profile of an orally administered API is highly dependent on the solubility of that compound in an aqueous medium.

When an API is given orally, it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. An API with poor aqueous solubility will typically exhibit "dissolution-rate-limited" absorption, while an API with poor membrane permeability will typically exhibit "permeation-rate-limited" absorption.

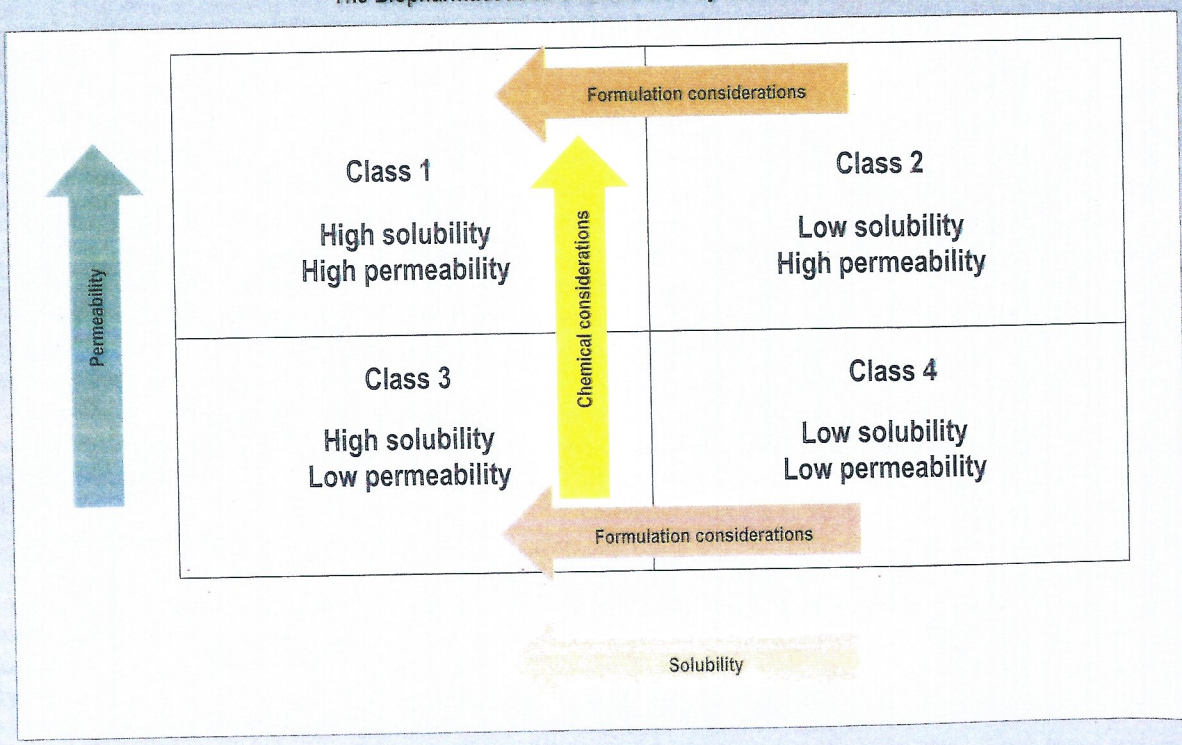
Bioavailability is a subcategory of absorption and represents the fraction of an administered dose of unchanged API that reaches systemic circulation. It is one of the principal pharmacokinetic properties of a drug product. Factors that affect bioavailability include the API's chemical and physical properties (e.g., solubility, particle size, physical form—crystalline or amorphous), stability, the drug product's formulation (immediate release versus extended or some type of modified release), the excipients the product includes, and how the product is manufactured.

Bioavailability may also be affected by gastric empting rate, i.e., insufficient time for absorption and the health of the GI tract, which may be affected by age, stress, surgery, metabolism differences, metabolism by luminal microflora, and/or fed versus fasted state.

Poorly soluble APIs often require high doses in order to reach a therapeutic effect after oral administration. This can

FIGURE 1

The Biopharmaceutics Classification System for APIs



increase side effects. Some insoluble APIs cannot be delivered orally at all. Consequently, poor aqueous solubility remains a major problem when formulating NCEs into oral drug products.

Advantages of solubility enhancement include faster absorption, greater bioavailability, and better efficacy. Better solubility can also reduce the dosage and thus unpleasant side effects. That, in turn, can improve patient compliance.

Methods to improve bioavailability

There are several options for overcoming poor bioavailability. A pharmacokinetic approach may involve modifying, if possible, the chemical structure of the compound. Examples include preparing esters or various salts. A pharmaceutical approach may involve modifying the formulation, manufacturing process, or physicochemical properties of the API. With this approach, formulators generally focus on two areas: enhancing the solubility and dissolution rate of the API and/or enhancing permeability.

Enhancement strategies include adjusting pH, reducing particle size, using surfactants, creating dispersions, and molecularly encapsulating the API.

Solubility refers to the maximum concentration of the API dissolved in a solvent under specific temperature, pH, and pressure. Solubility modification can be chemical or physical. Physical modification includes particle size reduction and/or changing the crystal habit from a crystalline form to a different polymorph or an amorphous form. The tendency of molecules to exist in different physical forms may be advantageous in some instances. For example, it may enable you to use a more soluble polymorph or amorphous form.

Adjustment of pH. Adjusting the pH is a simple and common method of increasing the aqueous solubility of an ionizable compound. It works because absorption depends largely on diffusion, which varies with the pH of the different regions of the GI tract, as well as the acid dissociation constant (pKa) and permeability of the API. The absorption process is moderated by the surface area of the region of release and its pH, which affects ionization of the API. If the pH of a drug product with low water solubility is changed, parts of the molecule that may be protonated (base) or deprotonated (acid) may acquire the potential to be dissolved in water. While parameters like salt selection and pH are considerations at the pre-formulation stage, using excipients to adjust the pH is an option during formulation development.

Particle size reduction. When reducing particle size to enhance solubility, you can choose from several dry and wet techniques. The choice may depend on the final particle size you're seeking. It's also essential to know the properties of the material because almost all techniques involve creating new surface ara and this requires adding energy proportional to the bonds holding the particles together. Is the material ductile or brittle? Brittle materials are easier to fracture.

Conventional dry reduction techniques use compression or impact. Compression mills work via moving jaws, rolls, or a gyratory cone. Roller mills can produce very fine particles. Impact mills uses either mechanical or fluid energy. Mechanical impact equipment includes hammermills, screen mills, pin mills, and air classifying mills. Fluid-energy impact equipment includes spiral jet mills and fluid-energy mills. Wet grinding is appropriate when fine particles, e.g. nanoparticles, are required or where an explosion or dust hazard exists. The fluid can be water, oil, or a nonaqueous solvent.

Surfactants. Using surfactants as solubilizing agents is another means to enhance solubility. The capacity of surfactants to solubilize an API depends on many factors, including the surfactant's chemical structure, the API's chemical structure, temperature, pH, and ionic strength. At low usage levels, surfactants may reduce surface energy of the API crystal to increase its solubilization rate. Nonionic surfactants are usually better solubilizing agents than ionic surfactants for hydrophobic APIs. With polar APIs, it's more complicated to establish a general relationship between the degree of solubilization and the chemical structure of the surfactant.

Dispersions If these basic techniques cannot suitably enhance bioavailability, other technologies, such as dispersions, may be appropriate. A solid dispersion is a mixture of one or more APIs in an inert carrier or matrix at a solid state. Because dispersions decrease particle size and/or increase surface area, they can improve the dissolution rate and bioavailability of poorly water-soluble APIs.

They're prepared by melting, by using a solvent, or by a using a melt-solvent method. Methods for preparing dispersions may include melt or melt-solvent techniques, precipitation, spray drying, and hot-melt extrusion. Upon exposure to an aqueous medium, the carrier in a solid dispersion dissolves and the API is released as very fine particles.

In a melt or melt-solvent process, an API is dissolved/dispersed in a molten carrier with or without the aid of a solvent. This mixture is cooled to form a solid mass that can then be further processed.

A spray-dried dispersion is a single-phase, amorphous molecular dispersion of an API in a carrier matrix. That is, the compound is molecularly "dissolved" in a solid matrix. This is achieved by combining the API and a solvent and then evaporating the solvent from droplets quickly enough to prevent phase separation or crystallization.

In solid amorphous dispersions, the API is adsorbed on to the surface of an insoluble material such as silicon dioxide, which has a large surface area. The result is an increase in the dispersion's surface area relative to the normal dispersion of the API. This allows rapid dissolution of the API, much faster than the unprocessed crystalline API.

Hot-melt extrusion applies heat, pressure, and agitation to combine materials and then forces the mixture through a

die. This method of dispersing poorly soluble APIs in a carrier system can increase dissolution rates and bioavailability. After cooling, the extruded mixture, or extrudate, generally consists of a single-phase matrix that can be milled to the desired particle size and incorporated into traditional tablets or capsules.

Molecular encapsulation. In more difficult situations, cyclodextrins have been shown to increase water solubility, dissolution rate and, consequently, bioavailability of insoluble APIs. Cyclodextrins are cyclic oligosaccharides that have been shown to form inclusion complexes via molecular encapsulation that involves a guest molecule, i.e., an API, confined within the cavity of the host cyclodextrin molecule. This complexation depends largely on the dimensions of the cyclodextrin and the particular steric arrangement of the functional groups of the API, which leads to a relatively hydrophilic exterior and a hydrophobic interior within the host molecule. These complexes can be formed by a number of standard processing techniques, including blending, precipitation, co-milling, and spray drying. *T&C*

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